GASTRO-HEP News

By Christina Lesica

Successful Pilot Trial Using Low-dose Naltrexone to Treat Crohn's Disease

Low-dose naltrexone (LDN) therapy appears to be effective and safe to treat patients with active Crohn's disease, according to an open-label prospective pilot trial, the results of which were published in the February issue of the *American Journal of Gastroenterology.*

Seventeen patients with active Crohn's disease and a mean Crohn's disease activity index (CDAI) score of 356 (±27) were enrolled in a 12-week trial and given oral naltrexone 4.5 mg daily. CDAI scores decreased significantly (P=.01) with LDN and remained lower than baseline 4 weeks after completing therapy. Eighty-nine percent of patients showed a response to LDN, and 67% of patients achieved remission (P<.001). Improvement was also recorded in inflammatory bowel disease questionnaires and short-form quality of life surveys with LDN compared to baseline. No laboratory abnormalities were noted. The most common side effect was sleep disturbances, which occurred in 7 patients.

"This is a novel, yet effective, approach to treating a common disease," said Jill Smith, MD, Professor of Gastroenterology at Pennsylvania State University College of Medicine, one of the lead investigators. A follow-up controlled trial, sponsored by the Broad Medical Foundation and the National Institutes of Health, has been launched by Dr. Smith and Ian Zagon, PhD, Professor of Neural and Behavioral Sciences at Pennsylvania State University, to confirm the results of the first study.

"Although it is a preliminary investigation and its findings need to be verified by controlled studies, it points to the efficacy of low-dose naltrexone in treating patients with Crohn's," said Dr. Zagon.

Naltrexone was initially approved by the FDA in 1984 for treating substance abuse. Endogenous opioids and opioid antagonists (which include naltrexone) have been shown to play a role in healing and repair of tissues.

Positive Results in Barrett Esophagus Trial With Radiofrequency Therapy

Study results published in the February issue of *Gastrointestinal Endoscopy* reported on 100 patients with the earliest stage of Barrett esophagus who received ablation using the HALO360 Ablation System, a balloon-based radiofrequency device designed to remove diseased cells using controlled heat. At 1-year follow-up, 70% of patients enrolled in this multicenter clinical trial were free of Barrett esophagus.

The procedures were performed endoscopically. Follow-up visits over 12 months included frequent endoscopy with biopsy to determine if the disease was fully eliminated. At 1 year, 70% of patients showed no evidence of Barrett esophagus, whereas the remaining patients had near-complete resolution of their disease.

Lead author Virender K. Sharma, MD, Associate Professor of Medicine at the Mayo Clinic in Scottsdale, Arizona, said, "Until now, the patient with Barrett esophagus was relegated to a lifetime of frequent endoscopic surveillance procedures to watch for progression to more dangerous forms of the disease like dysplasia and cancer. The results of this study suggest that we can safely and proactively eliminate Barrett esophagus at the very earliest stage, rather than limiting ourselves to passive observation of the disease for progression."

Trial of Sorafenib in Hepatocellular Carcinoma (HCC) Stopped Early

An independent data monitoring committee (DMC) concluded that the phase III trial for sorafenib (Nexavar, Bayer/Onyx) in patients with advanced HCC met its primary endpoint, resulting in superior overall survival in patients receiving sorafenib tablets versus those patients receiving placebo. The DMC also noted that there was no demonstrated difference in serious adverse event rates between the two treatment arms. Based on these conclusions, it was recommended that the trial be stopped early. All patients enrolled in the trial were granted access to sorafenib.

This analysis was conducted using data from the Sorafenib HCC Assessment Randomized Protocol (SHARP) Trial, an international phase III double-blind, randomized, placebo-controlled trial designed to evaluate sorafenib in patients with advanced HCC who had no prior systemic therapy. The primary endpoint of the study, which randomized 602 patients, compared overall survival and time-to-symptom-progression in patients who were administered sorafenib versus those patients administered placebo.

The incidence of bleeding regardless of causality was 15% for sorafenib versus 8% for placebo, and the incidence of treatment-emergent cardiac ischemia/infarction was 2.9% for sorafenib versus 0.4% for placebo. The most common treatment-emergent adverse events with sorafenib were diarrhea, rash/desquamation,

fatigue, hand-foot skin reaction, alopecia, and nausea. Grade 3/4 adverse events were 38% for sorafenib versus 28% for placebo.

"The observed superiority in overall survival for [sorafenib]-treated patients over patients receiving placebo demonstrates the efficacy of [sorafenib] in advanced primary liver cancer," said Jordi Bruix, MD, coprincipal investigator and head of the Barcelona Clinic Liver Cancer Group, Liver Unit, Hospital Clinic Barcelona, Spain.

Sorafenib is currently approved in the United States for the treatment of patients with advanced kidney cancer. The process of filing with the FDA and European health authorities for approval for the treatment of HCC will be started immediately.

Yeast-based Probiotic Shown to Significantly Reduce Recurrence of Intestinal Disease

Probiotic therapy has been clinically proven to assist in the prevention and management of antibiotic-associated diarrhea, but recent analysis concludes that only the yeast-based probiotic *Saccharomyces boulardii* (Florastor, Biocodex), combined with antibiotic therapy, is effective against the recurrence of the severe intestinal disease brought on by the *Clostridium difficile* pathogen.

C. difficile–associated disease (CDAD) is treatable with powerful antibiotics such as metronidazole or vancomycin, but because *C. difficile* is a spore-producing pathogen, patients often suffer from relapse when the spores "hatch" weeks or even months later. New studies suggest that the incidence of recurrent CDAD symptoms can be avoided by combining traditional antibiotic therapy with *S. boulardii.*

"Almost one in four CDAD patients will experience a recurrence of symptoms after a round of antibiotic therapy," said Patricia Raymond, MD, Associate Professor of Clinical Medicine at Eastern Virginia Medical School. "When a relapse occurs, use of [*S. boulardii*] during the second antibiotic course can help protect against future relapses because it colonizes the gut … which can help fight recurrent *C. difficile.*"

C. difficile has been the subject of recent heightened concern in the medical community because although it had been commonly viewed as a problem contracted only during lengthy hospital stays, it has been occurring among healthy people in the community. Also of concern is a new, epidemic "super-strain" of *C. difficile*, *Clostridium Difficile NAP/027*, which, according to Dr. Raymond, produces 16 times more Toxin A and 23 times more Toxin B than other *C. difficile* strains.

Recombinant Human Lactoferrin and Lysozyme Helps Children Recover Faster From Diarrhea

Adding recombinant human lactoferrin (Lactiva, Ventria Bioscience) and recombinant human lysozyme (Lysomin, Ventria Bioscience) to standard electrolyte solution helped children recover 1.5 days faster than standard electrolyte solution alone, according to a study published in the February issue of the *Journal of Pediatric Gastroenterology and Nutrition*.

The double-blind study followed 140 children who were suffering from diarrhea and admitted to the hospital. The results found that children who took the electrolyte solution containing lactoferrin and lysozyme recovered in an average of 3.67 days compared to children who took electrolyte solution alone who recovered in 5.21 days. In addition, children receiving lactoferrin and lysozyme were more likely to recover from their diarrhea and were less likely to relapse into another episode of diarrhea.

Decades-Long Study On Surgery for Crohn's Disease

Decades of research have recently yielded an in-depth look at the management of bowel stricture recurrence in patients who undergo surgery for Crohn's disease. Published in *Surgery*, this prospective, longitudinal study was conducted by Fabrizio Michelassi, MD, Chairman of the Department of Surgery and the Lewis Atterbury Stimson Professor of Surgery at Weill Cornell Medical College, and Surgeon-in-Chief at New York-Presbyterian Hospital/Weill Cornell Medical Center in New York City.

Starting with the first patient he operated on with Crohn's disease in 1988, Dr. Michelassi kept records on 981 patients who underwent a total of 1,132 procedures, 668 of which involved recurrent disease. During each procedure, Dr. Michelassi took pictures and made detailed sketches of the areas subject to surgery. "If these patients came to me again 5 or 10 years later with a stricture recurrence, I could compare the location of the recurrence to the site of the original surgery," he said.

In the past, Crohn's patients typically underwent surgical removal of the bowel at the point of stricture, although in recent years, corrective, bowel-sparing strictureplasties have become much more common. Up until now, however, surgeons lacked good information on the long-term consequences of these operations compared with resection.

"There's never been anything before done on this scale, or with this level of precision. That's meant that—up until now—surgical management of this disease has been largely a matter of guesswork," Dr. Michelassi said.

The study found that strictureplasty is less likely to lead to stricture recurrence later on, compared to resection of the stricture. "First of all, it validated the notion that strictureplasty carries a lower risk of stricture recurrence compared to resection," Dr. Michelassi says. "And if a recurrence does occur after strictureplasty, it is likely to happen much later than after resection." Recurrences after strictureplasty were also less likely to require a surgical excision of the affected area compared to recurrences occurring after resection.

The study also found that up to a third of recurrences occur away from the site of the original operation. Furthermore, the type and site of prior surgery appears to influence the pattern of recurrence, the study found. The study also provides new guidance on prophylactic strictureplasty.

"Sometimes we encounter a stricture that isn't giving the Crohn's patient any symptoms right now. We know, though, that these strictures can lead to trouble in about 25% of cases," Dr. Michelassi explains. "Based on our findings, we would now advise that if an asymptomatic stricture can be fixed using bowel-sparing strictureplasty, then the surgeon should go ahead and perform that type of prophylactic procedure. However, if fixing the problem requires bowel resection, then we would advise leaving the stricture alone, because there's still a 75% chance it will not cause the patient any harm."

In Brief

Dual endoscopic therapy proved significantly superior to epinephrine injection alone but had no advantage over thermal or mechanical monotherapy in improving the outcome of patients with high-risk peptic ulcer bleeding, according to meta-analysis of controlled trials. (*Am J Gastroenterol*. 2007; 102:279-289.)

Progression of fibrosis in patients with recurrent hepatitis C after liver transplantation under antiviral therapy is not linear over time, according to retrospective study. Occurrence of severe fibrosis is related to factors associated with immunosuppressive regimen, donor age, and past history of pretransplant antiviral therapy. (*Liver Transpl*. 2007;13:294-301.)

Combination therapy with ciprofloxacin and tinidazole was generally well tolerated and was effective in treating patients with chronic refractory pouchitis. (*Dis Colon Rectum*. 2007 Feb; [Epub ahead of print].)